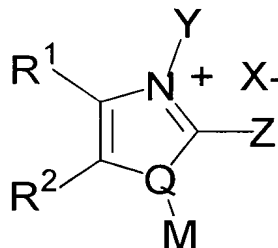


What is claimed:

1. A method of decreasing intraocular pressure or improving ocular accommodation in an animal, including a human, comprising administering an intraocular pressure
- 5 decreasing or accommodation improving amount of (A) a compound of the formula I:



(I)

wherein

a.  $R^1$  and  $R^2$  are

- 10 1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino,  $(C_1-C_3)$ alkylenedioxy, allyl, amino,  $\omega$ -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy,  $(C_2-C_6)$ hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl,
- 15 alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4- $[C_6 \text{ or } C_{10}]$ aryl piperidin-1-yl, 4- $[C_6 \text{ or } C_{10}]$ aryl piperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is  $C_6$  or  $C_{10}$  aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl
- 20 ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O,  $ArSO_2-$ ,  $ArSO-$ ,  $ArS-$ ,  $ArSO_2NH-$ ,  $ArNH$ ,  $(N-Ar)(N-alkyl)N-$ ,  $ArC(O)-$ ,  $ArC(O)NH-$ ,  $ArNH-C(O)-$ , and  $(N-Ar)(N-alkyl)N-C(O)-$ , or together  $R_1$  and  $R_2$  comprise methylenedioxy; or
- 25 2. together with their ring carbons form a  $C_6-$  or  $C_{10}-$  aromatic fused ring system; or

3. together with their ring carbons form a C<sub>5</sub>-C<sub>7</sub> fused cycloalkyl ring having up to two double bonds including any fused double bond of the -olium or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups; or
5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)<sub>n</sub>, where n=0, 1, or 2;

**b. Z is**

1. hydrogen, alkyl, Ar—CH<sub>2</sub>;
2. a group of the formula -NR<sup>3</sup>R<sup>4</sup>, wherein R<sup>3</sup> and R<sup>4</sup> may be independently hydrogen, alkyl, Ar, or Ar—alkyl-;
3. a group of the formula -CH(OR<sup>11</sup>)R<sup>12</sup>, wherein R<sup>11</sup> is hydrogen, methyl, ethyl or CH<sub>3</sub>C(O)-; and R<sup>12</sup> is [C<sub>1</sub> to C<sub>6</sub>]alkyl, Ar, or CO<sub>2</sub>R<sup>13</sup> wherein R<sup>13</sup> is hydrogen methyl or ethyl;
4. a group of the formula -C(CO<sub>2</sub>R<sup>13</sup>)(OR<sup>11</sup>)R<sup>12</sup>
5. a group of the formula -CH<sub>2</sub>WAr, wherein W is -(C=O)- or -S(O)<sub>n</sub>- where n=1 or 2; or
6. a group of the formula -CH<sub>2</sub>C≡C-R<sup>14</sup>, wherein R<sup>14</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl;

**c. Y is**

1. amino, or
2. a group of the formula -CH(R<sup>5</sup>)-R<sup>6</sup> wherein
  - (a) R<sup>5</sup> is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C<sub>6</sub> or C<sub>10</sub>]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinyllalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-ylalkyl, 4-[C<sub>6</sub> or

C<sub>10</sub>]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C<sub>6</sub> or C<sub>10</sub>]aryl, or independently the same as R<sup>6</sup>;

(b) R<sup>6</sup> is

- 5 (1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C<sub>6</sub> or C<sub>10</sub> aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or
- 10 (2) a group of the formula -W-R<sup>7</sup>, wherein R<sup>7</sup> is alkyl, alkoxy, hydroxy or Rs, wherein W is -C(=O)- or -S(O)<sub>n</sub>- where n=1 or 2;
- (3) a group of the formula -W-OR<sup>8</sup> wherein R<sup>8</sup> is hydrogen or alkyl,
- (4) a group of the formula -CH(OH)Rs; or
- (5) a group of the formula -W-N(R<sup>9</sup>)R<sup>10</sup>, wherein
- 15 [a] R<sup>9</sup> is hydrogen and R<sup>10</sup> is an alkyl or cycloalkyl, optionally substituted by
- (i) [C<sub>6</sub> or C<sub>10</sub>]aryl, or
- (ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups, or fused to a
- 20 substituted phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring, or
- 25 (iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or
- 30 [b] R<sup>9</sup> is hydrogen or lower alkyl and R<sup>10</sup> is Ar; or
- [c] R<sup>9</sup> is hydrogen or lower alkyl, and R<sup>10</sup> is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d] R<sup>9</sup> and R<sup>10</sup> are both alkyl groups; or

[e] R<sup>9</sup> and R<sup>10</sup> together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C<sub>6</sub>-or C<sub>10</sub>)aryl, (C<sub>6</sub>-or C<sub>10</sub>)arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy; or

[f] R<sup>9</sup> and R<sup>10</sup> are both hydrogen; or

d. Q is N, O or S;

e. M is absent when Q is O or S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio,

amino,  $\text{ArC(O)-}$ ,  $\text{ArO-}$ ,  $\text{Ar-}$ , carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

2. The method of claim 1, comprising administering an intraocular pressure  
5 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH(R}^5\text{)R}^6$ .
3. The method of claim 2, comprising administering an intraocular pressure  
10 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH(R}^5\text{)-W-R}^7$ .
4. The method of claim 2, comprising administering an intraocular pressure  
15 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH(R}^5\text{)-W-Rs}$ .
5. The method of Claim 1, comprising administering an intraocular pressure  
20 decreasing or accommodation improving amount of a compound of formula I, wherein  $\text{R}^1$  and  $\text{R}^2$  together with their ring carbons form a  $\text{C}_6$ - or  $\text{C}_{10}$ - aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfonic acid, alkylsulfonyl or  $\omega$ -alkylenesulfonic acid groups, or a  $\text{C}_1$ - $\text{C}_3$  alkylenedioxy group with the proviso that when Q is nitrogen  $\text{R}^1$  and  $\text{R}^2$  do not form a  $\text{C}_6$  fused aromatic ring.
6. The method of Claim 1, comprising administering an intraocular pressure  
25 decreasing amount of a compound of the compound of formula I, wherein Q is S, and Y and Z are both  $-\text{NH}_2$ .
7. The method of Claim 1, further comprising administering an effective amount of a cholinergic agent.
- 30 8. The method of Claim 1, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein  
a.  $\text{R}^1$  and  $\text{R}^2$  are

1003312-123401

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, allyl,  $\omega$ -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar {wherein, consistent with the rules of aromaticity, Ar is C<sub>6</sub> or C<sub>10</sub> aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O, ArSO<sub>2</sub>-, ArSO-, ArS-, ArSO<sub>2</sub>NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-; or
2. together with their ring carbons form a C<sub>6</sub>- or C<sub>10</sub>- aromatic fused ring system; or
3. together with their ring carbons form a C<sub>5</sub>-C<sub>7</sub> fused cycloalkyl ring having up to two double bonds including any fused double bond of the -olium or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups; or
5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)<sub>n</sub>, where n=0, 1, or 2;
- b. Z is
1. hydrogen, alkyl, Ar-CH<sub>2</sub>;
2. a group of the formula -NR<sup>3</sup>R<sup>4</sup>, wherein R<sup>3</sup> and R<sup>4</sup> may be independently hydrogen, alkyl, Ar, or Ar-alkyl-;

3. a group of the formula  $-\text{CH}(\text{OR}^{11})\text{R}^{12}$ , wherein  $\text{R}^{11}$  is hydrogen, methyl, ethyl or  $\text{CH}_3\text{C}(\text{O})-$ ; and  $\text{R}^{12}$  is  $[\text{C}_1 \text{ to } \text{C}_6]\text{alkyl}$ ,  $\text{Ar}$ , or  $\text{CO}_2\text{R}^{13}$  wherein  $\text{R}^{13}$  is hydrogen methyl or ethyl;
4. a group of the formula  $-\text{C}(\text{CO}_2\text{R}^{13})(\text{OR}^{11})\text{R}^{12}$
5. a group of the formula  $-\text{CH}_2\text{WAr}$ , wherein  $\text{W}$  is  $-(\text{C}=\text{O})-$  or  $-\text{S}(\text{O})_n-$  where  $n=1$  or  $2$ ; or
6. a group of the formula  $-\text{CH}_2\text{C}\equiv\text{C}-\text{R}^{14}$ , wherein  $\text{R}^{14}$  is  $(\text{C}_1-\text{C}_6)\text{alkyl}$ ;

c.  $\text{Y}$  is

1. amino, or

2. a group of the formula  $-\text{CH}(\text{R}^5)-\text{R}^6$  wherein

(a)  $\text{R}^5$  is hydrogen or alkyl;

(b)  $\text{R}^6$  is

(1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or  $\text{Rs}$ , wherein  $\text{Rs}$  is a  $\text{C}_6$  or  $\text{C}_{10}$  aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

(2) a group of the formula  $-\text{W}-\text{R}^7$ , wherein  $\text{R}^7$  is alkyl, alkoxy, hydroxy or  $\text{Rs}$ , wherein  $\text{W}$  is  $-(\text{C}=\text{O})-$  or  $-\text{S}(\text{O})_n-$  where  $n=1$  or  $2$ ;

(3) a group of the formula  $-\text{W}-\text{OR}^8$  wherein  $\text{R}^8$  is hydrogen or alkyl,

(4) a group of the formula  $-\text{CH}(\text{OH})\text{Rs}$ ; or

(5) a group of the formula  $-\text{W}-\text{N}(\text{R}^9)\text{R}^{10}$ , wherein

[a]  $\text{R}^9$  is hydrogen and  $\text{R}^{10}$  is an alkyl or cycloalkyl, optionally substituted by

(i)  $[\text{C}_6 \text{ or } \text{C}_{10}]\text{aryl}$ , or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of  $\text{N}$ , and the 5-membered heteroaryl ring contains from one to three atoms of  $\text{N}$  or one atom of  $\text{O}$  or  $\text{S}$  and zero to two atoms of  $\text{N}$ , said heteroaryl ring can be optionally substituted with one or more halo or  $(\text{C}_1-\text{C}_3)\text{alkylenedioxy}$  groups, or fused to a substituted phenyl, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R<sup>9</sup> is hydrogen or lower alkyl and R<sup>10</sup> is Ar; or

[c] R<sup>9</sup> is hydrogen or lower alkyl, and R<sup>10</sup> is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

5 [d] R<sup>9</sup> and R<sup>10</sup> are both alkyl groups; or

[e] R<sup>9</sup> and R<sup>10</sup> together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C<sub>6</sub>-or C<sub>10</sub>)aryl, (C<sub>6</sub>-or C<sub>10</sub>)arylalkyl, or a 10 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy; or

15 [f] R<sup>9</sup> and R<sup>10</sup> are both hydrogen; or

d. Q is N, O or S;

e. M is absent when Q is O or S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

20 (B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω- 25 alkylenesulfonic acid, alkylthio, allyl, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid; and

wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, 30 alkoxycarbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

1003812-133401



9. The method of claim 8, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH}(\text{R}^5)\text{R}^6$ .
- 5 10. The method of claim 9, comprising administering an intraocular pressure decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH}(\text{R}^5)-\text{W}-\text{R}^7$ .
11. The method of claim 9, comprising administering an intraocular pressure  
10 decreasing or accommodation improving amount of a compound of formula I, wherein Y is according to formula  $-\text{CH}(\text{R}^5)-\text{W}-\text{Rs}$ .
12. The method of Claim 1, comprising administering an intraocular pressure decreasing amount of a compound of the compound of formula I, wherein Q is S, Y and  
15 Z are both  $-\text{NH}_2$ .

1003812-133101